CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40224

APPROVAL LETTER

ANDA 40-224

JAN 26 1999

Pharmaceutical Associates, Inc.
Attention: Kaye McDonald
P.O. Box 128
Conestee, SC 29636

Dear Madam:

This is in reference to your abbreviated new drug application dated November 25, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Chlorpromazine Hydrochloride Oral Concentrate USP, 100 mg/mL.

Reference is also made to your amendments dated November 30, December 10, December 16 and December 22, 1998; and January 11 and January 13, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Chlorpromazine Hydrochloride Oral Concentrate USP, 100 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Thorazine® Oral Concentrate, 100 mg/mL of SmithKline Beecham Pharmaceuticals).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 1/26/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40224

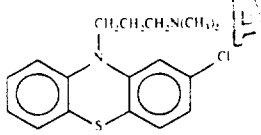
DRAFT FINAL PRINTED LABELING

Chlorpromazine Hydrochloride Oral Concentrate, USP

tranquilizer • antiemetic

DESCRIPTION

Chlorpromazine hydrochloride, a dimethylamine derivative of phenothiazine, has the chemical name 2-Chloro-10-[3-(dimethylamino)propyl]phenothiazine monohydrochloride. It has the following structural formula:



355.33 $C_{17}H_{19}ClN_2S \cdot HCl$

Chlorpromazine hydrochloride occurs as white or slightly creamy white, odorless, crystalline powder which darkens on prolonged exposure to light.

Each mL, for oral administration, contains 100 mg chlorpromazine hydrochloride. Inactive ingredients consist of edetate calcium disodium, citric acid, sodium bisulfite, ascorbic acid, glycerin, vanilla, propylene glycol, saccharin sodium, sodium benzoate, and water. Sodium hydroxide as needed to adjust pH.

CLINICAL PHARMACOLOGY

The precise mechanism whereby the therapeutic effects of chlorpromazine are produced is not known. The principal pharmacological actions are psychotropic. It also exerts sedative and antiemetic activity. Chlorpromazine has actions at all levels of the central nervous system—primarily at subcortical levels—as well as on multiple organ systems. Chlorpromazine has strong antiadrenergic and weaker peripheral anticholinergic activity; ganglionic blocking action is relatively slight. It also possesses slight antihistaminic and antiserotonin activity.

INDICATIONS AND USAGE

For the management of manifestations of psychotic disorders.

To control nausea and vomiting.

For relief of restlessness and apprehension before surgery.

For acute intermittent porphyria.

To control the manifestations of the manic type of manic-depressive illness.

For relief of intractable hiccups.

For the treatment of severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations), and in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability and poor frustration tolerance.

CONTRAINDICATIONS

Do not use in comatose states or in the presence of large amounts of central nervous system depressants (alcohol, barbiturates, narcotics, etc.).

WARNINGS

The extrapyramidal symptoms which can occur secondary to chlorpromazine may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g., Reye's syndrome or other encephalopathy. The use of chlorpromazine and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on PRECAUTIONS and ADVERSE REACTIONS.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of anti-psychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Patients with bone marrow depression or who have previously demonstrated a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) with a phenothiazine should not receive any phenothiazine, including chlorpromazine, unless in the judgment of the physician the potential benefits of treatment outweigh the possible hazard.

Chlorpromazine may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, caution patients about activities requiring alertness (e.g., operating vehicles or machinery).

The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

Chlorpromazine may counteract the antihypertensive effect of guanethidine and related compounds.

Usage in Pregnancy: Safety for the use of chlorpromazine during pregnancy has not been established. Therefore, it is not recommended that the drug be given to pregnant patients except when, in the judgment of the physician, it is essential. The potential benefits should clearly outweigh possible hazards. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.

Reproductive studies in rodents have demonstrated potential for embryotoxicity, increased neonatal mortality and nursing transfer of the drug. Tests in the offspring of the drug-treated rodents demonstrate decreased performance. The possibility of permanent neurological damage cannot be excluded.

Nursing Mothers: There is evidence that chlorpromazine is excreted in the breast milk of nursing mothers
Other: The concentrate contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

General

Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Chlorpromazine should be administered cautiously to persons with cardiovascular, liver, or renal disease. There is evidence that patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the CNS effects of chlorpromazine (i.e., impaired cerebration and abnormal slowing of the EEG).

Because of its CNS depressant effect, chlorpromazine should be used with caution in patients with chronic respiratory disorders such as severe asthma, emphysema and acute respiratory infections, particularly in children.

Because chlorpromazine can suppress the cough reflex, aspiration of vomitus is possible.

Chlorpromazine prolongs and intensifies the action of CNS depressants such as anesthetics, barbiturates and narcotics. When chlorpromazine is administered concomitantly, about ¼ to ½ the usual dosage of such agents is required. When chlorpromazine is not being administered to reduce requirements of CNS depressants, it is best to stop such depressants before starting chlorpromazine treatment. These agents may subsequently be reinstated at low doses and increased as needed.

Note: Chlorpromazine does *not* intensify the anticonvulsant action of barbiturates. Therefore, dosage of anticonvulsants, including barbiturates should *not* be reduced if chlorpromazine is started. Instead, start chlorpromazine at low doses and increase as needed.

Use with caution in persons who will be exposed to extreme heat, organophosphorus insecticides, and in persons receiving atropine or related drugs.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately 1/3 of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescribing of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics.

As with all drugs which exert an anticholinergic effect, and/or cause mydriasis, chlorpromazine should be used with caution in patients with glaucoma.

Chlorpromazine diminishes the effect of oral anticoagulants.

Phenothiazines can produce alpha-adrenergic blockade.

Chlorpromazine may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Potentiation of anticonvulsant effects does not occur. However, it has been reported that chlorpromazine may interfere with the metabolism of phenytoin and thus precipitate phenytoin toxicity.

Concomitant administration with propranolol results in increased plasma levels of both drugs.

Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.

The presence of phenothiazines may produce false-positive phenylketonuria (PKU) test results.

Drugs which lower the seizure threshold, including phenothiazine derivatives, should not be used with metrizamide. As with other phenothiazine derivatives, chlorpromazine should be discontinued at least 48 hours before myelography, should not be resumed for at least 24 hours postprocedure, and should not be used for the control of nausea and vomiting occurring either prior to myelography or post-procedure with metrizamide.

Long-Term Therapy: To lessen the likelihood of adverse reactions related to cumulative drug effect, patients with a history of long-term therapy with chlorpromazine and/or other neuroleptics should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

Antiemetic Effect: The antiemetic action of chlorpromazine may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome. (See WARNINGS.)

When chlorpromazine is used with cancer chemotherapeutic drugs, vomiting as a sign of the toxicity of these agents may be obscured by the antiemetic effect of chlorpromazine.

Abrupt Withdrawal: Like other phenothiazines, chlorpromazine is not known to cause psychic dependence and does not produce tolerance or addiction. There may be, however, following abrupt withdrawal of high-dose therapy, some symptoms resembling those of physical dependence such as gastritis, nausea and vomiting, dizziness and tremulousness. These symptoms can usually be avoided or reduced by gradual reduction of the dosage or by continuing concomitant anti-parkinsonism agents for several weeks after chlorpromazine is withdrawn.

ADVERSE REACTIONS

Note: Some adverse effects of chlorpromazine may be more likely to occur, or occur with greater intensity, in patients with special medical problems, e.g., patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses.

Drowsiness, usually mild to moderate, may occur, particularly during the first or second week, after which it generally disappears. If troublesome, dosage may be lowered.

Jaundice: Overall incidence has been low, regardless of indication or dosage. Most investigators conclude it is a sensitivity reaction. Most cases occur between the second and fourth weeks of therapy. The clinical picture resembles infectious hepatitis, with laboratory features of obstructive jaundice, rather than those of parenchymal damage. It is usually promptly reversible on withdrawal of the medication; however, chronic jaundice has been reported.

There is no conclusive evidence that preexisting liver disease makes patients more susceptible to jaundice. Alcoholics with cirrhosis have been successfully treated with chlorpromazine without complications. Nevertheless, the medication should be used cautiously in patients with liver disease. Patients who have experienced jaundice with a phenothiazine should not, if possible, be reexposed to chlorpromazine or other phenothiazines.

If fever with grippe-like symptoms occurs, appropriate liver studies should be conducted. If tests indicate an abnormality, stop treatment.

Liver function tests in jaundice induced by the drug may mimic extrahepatic obstruction; withhold exploratory laparotomy until extrahepatic obstruction is confirmed.

Hematological Disorders, including agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia have been reported.

Agranulocytosis — Warn patients to report the sudden appearance of sore throat or other signs of infection. If white blood cell and differential counts indicate cellular depression, stop treatment and start antibiotic and other suitable therapy.

Most cases have occurred between the fourth and tenth weeks of therapy; patients should be watched closely during that period.

Moderate suppression of white blood cells is not an indication for stopping treatment unless accompanied by the symptoms described above.

Cardiovascular:

Hypotensive Effects - Postural hypotension, simple tachycardia, momentary fainting and dizziness may occur rarely, after the first oral dose. Usually recovery is spontaneous and symptoms disappear within ½ to 2 hours. Occasionally, these effects may be more severe and prolonged, producing a shock-like condition.

To control hypotension, place patient in head-low position with legs raised. If a vasoconstrictor is required, norepinephrine and phenylephrine are the most suitable. Other pressor agents, including epinephrine, should not be used as they may cause a paradoxical further lowering of blood pressure.

EKG Changes-particularly nonspecific, usually reversible Q and T wave distortions-have been observed in some patients receiving phenothiazine tranquilizers, including chlorpromazine.
Note: Sudden death, apparently due to cardiac arrest, has been reported.
CNS Reactions:
Neuromuscular (Extrapyramidal) Reactions-Neuromuscular reactions include dystonias, motor restlessness, pseudo-parkinsonism and tardive dyskinesia, and appear to be dose-related. They are discussed in the following paragraphs:
Dystonias: Symptoms may include spasm of the neck muscles, sometimes progressing to acute, reversible torticollis; extensor rigidity of back muscles, sometimes progressing to opisthotonos; carpopedal spasm; trismus swallowing difficulty; oculogyric crisis and protrusion of the tongue.
These usually subside within a few hours, and almost always within 24 to 48 hours after the drug has been discontinued.
In mild cases, reassurance or a barbiturate is often sufficient. *In moderate cases*, barbiturates will usually bring rapid relief. *In more severe adult cases*, the administration of an anti-parkinsonism agent, except levodopa (see PDR), usually produces rapid reversal of symptoms. *In children*, reassurance and barbiturates will usually control symptoms. (Or, parenteral diphenhydramine hydrochloride may be useful. See diphenhydramine hydrochloride prescribing information for appropriate children's dosage.) If appropriate treatment with anti-parkinsonism agents or diphenhydramine hydrochloride fails to reverse the signs and symptoms, the diagnosis should be reevaluated. Suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed when needed. If therapy is reinstituted, it should be at a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should not be reinstituted.
Motor Restlessness: Symptoms may include agitation or jitteriness and sometimes insomnia. These symptoms often disappear spontaneously. At times these symptoms may be similar to the original neurotic or psychotic symptoms. Dosage should not be increased until these side effects have subsided.
If these symptoms become too troublesome, they can usually be controlled by a reduction of dosage or change of drug. Treatment with anti-parkinsonian agents, benzodiazepines or propranolol may be helpful.
Pseudo-parkinsonism: Symptoms may include: mask-like facies, drooling, tremors, pillrolling motion, cogwheel rigidity and shuffling gait. In most cases these symptoms are readily controlled when an anti-parkinsonism agent is administered concomitantly. Anti-parkinsonism agents should be used only when required. Generally, therapy of a few weeks to 2 or 3 months will suffice. After this time patients should be evaluated to determine their need for continued treatment. (Note: Levodopa has not been found effective in neuroleptic-induced pseudo-parkinsonism.) Occasionally it is necessary to lower the dosage of chlorpromazine or to discontinue the drug.
Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The syndrome can also develop, although much less frequently, after relatively brief treatment periods at low doses. This syndrome appears in all age groups. Although its prevalence appears to be highest among elderly patients, especially elderly women, it is impossible to rely upon prevalence estimates to predict at the inception of neuroleptic treatment which patients are likely to develop the syndrome. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. In rare instances, these involuntary movements of the extremities are the only manifestations of tardive dyskinesia. A variant of tardive dyskinesia, tardive dystonia, has also been described.
There is no known effective treatment for tardive dyskinesia; anti-parkinsonism agents do not alleviate the symptoms of this syndrome. If clinically feasible, it is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.
It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.
Adverse Behavioral Effects-Psychotic symptoms and catatonic-like states have been reported rarely.
Other CNS Effects- Cerebral edema has been reported.
Convulsive seizures (*petit mal* and *grand mal*) have been reported, particularly in patients with EEG abnormalities or history of such disorders.
Abnormality of the cerebrospinal fluid proteins has also been reported.
Allergic Reactions of a mild urticarial type or photosensitivity are seen. Avoid undue exposure to sun. More severe reactions, including exfoliative dermatitis, have been reported occasionally.
Contact dermatitis has been reported in nursing personnel; accordingly, the use of rubber gloves when administering chlorpromazine liquid is recommended.
In addition, asthma, laryngeal edema, angioneurotic edema and anaphylactoid reactions have been reported.
Endocrine Disorders: Lactation and moderate breast engorgement may occur in females on large doses. If persistent, lower dosage or withdraw drug. False-positive pregnancy tests have been reported, but are less likely to occur when a serum test is used. Amenorrhea and gynecomastia have also been reported. Hyperglycemia, hypoglycemia and glycosuria have been reported.
Autonomic Reactions: Occasional dry mouth; nasal congestion; nausea; obstipation; constipation; adynamic ileus; urinary retention; priapism; miosis and mydriasis, atonic colon, ejaculatory disorders/impotence.
Special Considerations in Long-Term Therapy: Skin pigmentation and ocular changes have occurred in some patients taking substantial doses of chlorpromazine for prolonged periods.
Skin Pigmentation-Rare instances of skin pigmentation have been observed in hospitalized mental patients, primarily females who have received the drug usually for 3 years of more in dosages ranging from 500 mg to 1500 mg daily. The pigmentary changes, restricted to exposed areas of the body, range from an almost imperceptible darkening of the skin to a slate gray color, sometimes with a violet hue. Histological examination reveals a pigment, chiefly in the dermis, which is probably a melanin-like complex. The pigmentation may fade following discontinuance of the drug.
Ocular Changes-Ocular changes have occurred more frequently than skin pigmentation and have been observed both in pigmented and nonpigmented patients receiving chlorpromazine usually for 2 years or more in dosages of 300 mg daily and higher. Eye changes are characterized by deposition of fine particulate matter in the lens and cornea. In more advanced cases, star-shaped opacities have also been observed in the anterior portion of the lens. The nature of the eye deposits has not yet been determined. A small number of patients with more severe ocular changes have had some visual impairment. In addition to these corneal and lenticular changes, epithelial keratopathy and pigmentary retinopathy have been reported. Reports suggest that the eye lesions may regress after withdrawal of the drug.
Since the occurrence of eye changes seems to be related to dosage levels and/or duration of therapy, it is suggested that long-term patients on moderate to high dosage levels have periodic ocular examinations.
Etiology-The etiology of both of these reactions is not clear, but exposure to light, along with dosage/duration of therapy, appears to be the most significant factor. If either of these reactions is observed, the physician should weigh the benefits of continued therapy against the possible risks and, on the merits of the individual case, determine whether or not to continue present therapy, lower the dosage or withdraw the drug.
Other Adverse Reactions: Mild fever may occur after large I.M. doses. Hyperpyrexia has been reported. Increases in appetite and weight sometimes occur. Peripheral edema and a systemic lupus erythematosus-like syndrome have been reported.
Note: There have been occasional reports of sudden death in patients receiving phenothiazines. In some cases, the cause appeared to be cardiac arrest or asphyxia due to failure of the cough reflex.

OVERDOSAGE

(See also ADVERSE REACTIONS)

SYMPTOMS-Primarily symptoms of central nervous system depression to the point of somnolence or coma. Hypotension and extrapyramidal symptoms.

Other possible manifestations include agitation and restlessness, convulsions, fever, autonomic reactions such as dry mouth and ileus, EKG changes and cardiac arrhythmias.

TREATMENT-It is important to determine other medications taken by the patient since multiple drug therapy is common in overdosage situations. Treatment is essentially symptomatic and supportive. Early gastric lavage is helpful. Keep patient under observation and maintain an open airway, since involvement of the extrapyramidal mechanism may produce dysphagia and respiratory difficulty in severe overdosage. **Do not attempt to induce emesis because a dystonic reaction of the head or neck may develop that could result in aspiration of vomitus.** Extrapyramidal symptoms may be treated with anti-parkinsonism drugs, barbiturates, or diphenhydramine hydrochloride. See prescribing information for these products. Care should be taken to avoid increasing respiratory depression.

If administration of a stimulant is desirable, amphetamine, dextroamphetamine, or caffeine with sodium benzoate is recommended. Stimulants that may cause convulsions (e.g., picrotoxin or pentylenetetrazol) should be avoided.

If hypotension occurs, the standard measures for managing circulatory shock should be initiated. If it is desirable to administer a vasoconstrictor, norepinephrine and phenylephrine are most suitable. Other pressor agents, including epinephrine, are not recommended because phenothiazine derivatives may reverse the usual elevating action of these agents and cause a further lowering of blood pressure.

Limited experience indicates that phenothiazines are *not* dialyzable.

DOSAGE AND ADMINISTRATION-ADULTS

Adjust dosage to individual and the severity of his condition, recognizing that the milligram for milligram potency relationship among all dosage forms has not been precisely established clinically. It is important to increase dosage until symptoms are controlled. Dosage should be increased more gradually in debilitated or emaciated patients. In continued therapy, gradually reduce dosage to the lowest effective maintenance level, after symptoms have been controlled for a reasonable period.

Elderly Patients-In general, dosages in the lower range are sufficient for most elderly patients. Since they appear to be more susceptible to hypotension and neuromuscular reactions, such patients should be observed closely. Dosage should be tailored to the individual, response carefully monitored, and dosage adjusted accordingly. Dosage should be increased more gradually in elderly patients.

Psychotic Disorders-Increase dosage gradually until symptoms are controlled. Maximum improvement may not be seen for weeks or even months. Continue optimum dosage for 2 weeks; then gradually reduce dosage to the lowest effective maintenance level. Daily dosage of 200 mg is not unusual. Some patients require higher dosages (e.g., 800 mg daily is not uncommon in discharged mental patients).

HOSPITALIZED PATIENTS: ACUTELY DISTURBED OR MANIC - Parenteral therapy is indicated until patient is controlled. Usually patient becomes quiet and cooperative within 24 to 48 hours and oral doses may be substituted and increased until the patient is calm. 500 mg a day is generally sufficient. While gradual increases to 2,000 mg a day or more may be necessary, there is usually little therapeutic gain to be achieved by exceeding 1,000 mg a day for extended periods. In general, dosage levels should be lower in the elderly, the emaciated and the debilitated.

LESS ACUTELY DISTURBED- 25 mg t.i.d. Increase gradually until effective dose is reached-usually 400 mg daily.

OUTPATIENTS- 10 mg t.i.d. or q.i.d., or 25 mg b.i.d. or t.i.d. MORE SEVERE CASES- 25 mg t.i.d. After 1 or 2 days, daily dosage may be increased by 20 to 50 mg at semiweekly intervals until patient becomes calm and cooperative.

PROMPT CONTROL OF SEVERE SYMPTOMS- Initial treatment should be with intramuscular chlorpromazine. Subsequent doses should be oral, 25 to 50 mg t.i.d.

Nausea and Vomiting- 10 to 25 mg q4 to 6h, p.r.n., increased, if necessary.

Preurgical Apprehension- 25 to 50 mg, 2 to 3 hours before the operation.

Intractable Hiccups- 25 to 50 mg t.i.d. or q.i.d.. If symptoms persist for 2 to 3 days, parenteral therapy is indicated.

Acute Intermittent Porphyria- 25 to 50 mg t.i.d. or q.i.d. Can usually be discontinued after several weeks, but maintenance therapy may be necessary for some patients.

DOSAGE AND ADMINISTRATION-CHILDREN

Chlorpromazine should generally not be used in children under 6 months of age except where potentially lifesaving. It should not be used in conditions for which specific children's dosages have not been established.

Severe Behavioral Problems-OUTPATIENTS-Select route of administration according to severity of patient's condition and increase dosage gradually as required. Oral: ¼ mg/lb body weight q4 to 6h, p.r.n. (e.g., for 40 lb child-10 mg q4 to 6h).

HOSPITALIZED PATIENTS-As with outpatients, start with low doses and increase dosage gradually. In severe behavior disorders or psychotic conditions, higher dosages (50 to 100 mg daily, and in older children, 200 mg daily or more) may be necessary. There is little evidence that behavior improvement in severely disturbed mentally retarded patients is further enhanced by doses beyond 500 mg per day.

Nausea and Vomiting-Dosage and frequency of administration should be adjusted according to the severity of the symptoms and response of the patient. The duration of activity following intramuscular administration may last up to 12 hours. Subsequent doses may be given by the same route if necessary. Oral: ¼ mg/lb body weight (e.g., 40 lb child-10 mg q4 to 6h).

Preurgical Apprehension- Oral: ¼ mg/lb body weight, 2 to 3 hours before operation.

Note on Concentrate: When the Concentrate is to be used, add the desired dosage of Concentrate to 60 mL (2 fl oz) or more of diluent *just prior to administration*. This will insure palatability and stability. Vehicles suggested for dilution are tomato or fruit juice, milk, simple syrup, orange syrup, carbonated beverages, coffee, tea or water. Semisolid foods (soups, puddings, etc.) may also be used. The Concentrate is light sensitive; it should be protected from light and dispensed in amber bottles. *Refrigeration is not required.*

HOW SUPPLIED

Chlorpromazine Hydrochloride Oral Concentrate USP, 100 mg/mL is supplied as follows:

Concentrate: Intended for institutional use.

Clear, vanilla flavored liquid in 237 mL (8 fl oz) bottles with a calibrated dropper NDC 0121-0665-08

Store at controlled room temperature, 15°- 30°C (59° - 86°F) in tight, light-resistant containers.

The Concentrate form is light sensitive. For this reason it should be protected from light and dispensed in amber bottles. *Refrigeration is not required.*

CAUTION: Federal law prohibits dispensing without prescription.

Pal Pharmaceutical Associates, Inc.
Greenville, SC 29605

I 10/98

Mar 5

KEEP THIS END UP

100 mg/mL

Chlorpromazine Hydrochloride Oral Concentrate USP

NDC 0121-0665-08

Chlorpromazine Hydrochloride Oral Concentrate USP

100 mg/mL

Each mL contains Chlorpromazine Hydrochloride, 100 mg

DILUTE EACH DOSE BEFORE ADMINISTRATION.

PROTECT FROM LIGHT.

INTENDED FOR INSTITUTIONAL USE.

Rx ONLY

Store at controlled room temperature, 15°-30°C (59°-86°F).

237 mL (8 fl oz)

Important: Dispense in a tight, light-resistant bottle with graduated child-resistant dropper. Never dispense in a flint, green, or blue bottle. Bulk dilution for storage is not recommended.

Usual Dosage: 75 to 400 mg daily. (Doses of 100 mg or more b.i.d. or t.i.d. are for use only in severe neuropsychiatric conditions.) The concentrate is, mg for mg, therapeutically equivalent to other oral dosage forms of the drug. See accompanying insert for complete prescribing information.

Dilute each dose before administration.
Add dose to 60 mL (2 fl oz) or more of tomato or fruit juice, milk, simple syrup, orange syrup, carbonated beverages, coffee, tea or water.

Caution: Avoid direct contact with skin or clothes because of the possibility of contact dermatitis (skin reaction).
Wash thoroughly or change clothes if direct contact occurs.

CARTONS

CARTONS

047

NDC 0121-0665-08

Chlorpromazine Hydrochloride Oral Concentrate USP

100 mg/mL

Each mL contains Chlorpromazine Hydrochloride, 100 mg

DILUTE EACH DOSE BEFORE ADMINISTRATION.

PROTECT FROM LIGHT.

INTENDED FOR INSTITUTIONAL USE.

Rx ONLY

Store at controlled room temperature, 15°-30°C (59°-86°F).

237 mL (8 fl oz)

pai Pharmaceutical Associates, Inc.
Greenville, SC 29605

PHARMACIST: DO NOT REMOVE THIS LABEL

PATIENT INFORMATION

Caution: Avoid direct contact with skin or clothes because of the possibility of contact dermatitis (skin reaction). Wash thoroughly or change clothes if direct contact occurs.

Dilute each dose before administration. Add dose to 60 mL (2 fl oz) or more of tomato or fruit juice, milk, simple syrup, orange syrup, carbonated beverages, coffee, tea or water.

Dropper is graduated in 25 mg increments from 100 mg to 200 mg. To deliver 25 mg or 50 mg dose, fill dropper to 200 mg mark and dispense to 175 mg or 150 mg mark, respectively.

Important: Dispense in a tight, light-resistant bottle with graduated child-resistant dropper. Never dispense in a flint, green, or blue bottle. Bulk dilution for storage is not recommended.

Usual Dosage: 75 to 400 mg daily. (Doses of 100 mg or more b.i.d. or t.i.d. are for use only in severe neuropsychiatric conditions.) The concentrate is mg for mg therapeutically equivalent to other oral dosage forms of the drug. See accompanying insert for complete prescribing information.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40224

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 40-224

DRUG PRODUCT: Chlorpromazine HCl Oral Concentrate

FIRM: Pharmaceutical Associates, Inc.

DOSAGE FORM: Oral Concentrate **STRENGTH:** 100 mg/mL

CGMP: Statement/EIR Update Status:
The EER was found to be acceptable (1/12/98).

BIO: A waiver for the bioequivalence study was granted by the Division of Bioequivalence (Z. Wahba, 5/15/97).

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Chlorpromazine Hydrochloride Oral Concentrate USP, 100mg/mL is included in the US Pharmacopeia. Analytical method verification is acceptable (2/13/97).

STABILITY: (Are containers used in study identical to those in container section ?)
The containers used in the stability study are identical to those described in the container section.

LABELING:
Container, carton and insert labeling have been found satisfactory (Labeling approval summary 12/9/98, reviewed by L. Golson)

STERILIZATION VALIDATION (IF APPLICABLE):
Not Applicable

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
The size of bio batch was gallons (lot#13818). The proposed production size batch is gallons (max).
Source of NDS:
DMF Chlorpromazine Hydrochloride USP drug substance was found to be adequate (reviewed by Liang-Lii Huang, Ph.D., 12/11/98).

SIZE OF STABILITY BATCHES- (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
The exhibit batch (lot#13818) was the stability batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:
The proposed production batch is gallons (MAX) of the Chlorpromazine HCl Oral Concentrate 100 mg/mL. The manufacturing process will be the same as that of the exhibit batch.

CHEMIST: Liang-Lii Huang, Ph.D. **DATE:** December 22, 1998

SUPERVISOR: Paul Schwartz, Ph.D. **DATE:** December 23, 1998

cc:

ANDA 40-224
ANDA DUP 40-224
DIV FILE
Field Copy
HFD-600 /Reading File

Endorsements (Draft and Final with Dates):

HFD-627 / Liang-Lii Huang, Ph.D./ 12/22/98
HFD-627 /Paul Schwartz, Ph.D. / 12/23/98 PJ 1/4/99 12/23/98
HFD- /Division Director (final only)

X:\NEW\FIRMSNZ\PHARASSN\LTRS&REV\40224APP.SUM
Date: December 22, 1998

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMISTRY REVIEW NO. Three (3)

2. ANDA # 40-224

3. NAME AND ADDRESS OF APPLICANT
Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
P.O. Box 128
Conestee, SC 29636

4. LEGAL BASIS FOR SUBMISSION
The listed reference product is Thorazine® Concentrate 100 mg/mL Manufactured by SmithKline Beecham Pharmaceuticals. Thorazine® is not covered by any patent or exclusivity provisions.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Chlorpromazine HCl Oral Concentrate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
None

9. AMENDMENTS AND OTHER DATES:
Original: November 26, 1996
Amendment: April 14, 1998
Amendment: November 30, 1998
Telephone amendment: December 10,1998
Telephone amendment: December 16,1998
Telephone amendment: December 22,1998
Telephone amendment: January 11, 1999
Telephone amendment: January 13, 1999

10. PHARMACOLOGICAL CATEGORY
Antipsychotic

11. Rx or OTC

Rx

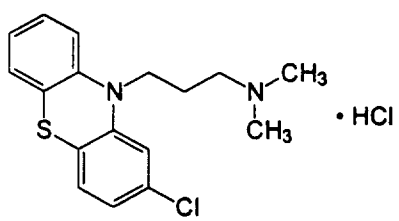
12. RELATED IND/NDA/DMF(s)

DMF#(type)	Product	DMF holder	LOA
	Chlorpromazine Hydrochloride		v 1.2, p133 v 2.2, p313,348 v 2.2, p343 V 2.2, p347 v 2.2, p352 v 2.2, p359 v 2.2, p358 v 2.2, p320 v 2.2, p419 v 2.2, p425 v 2.2, p433 v 2.2, p444 V 2.2, p449

13. DOSAGE FORM
Oral Concentrate

14. POTENCY
100 mg/mL

15. CHEMICAL NAME AND STRUCTURE
Name: Chlorpromazine Hydrochloride
Chemical name: 10*H*-Phenothiazine-10-propanamine, 2-chlor0-*N*,*N*-dimethyl-, monohydrochloride
CAS number: 69-09-0
Molecular weight: 355.33
Chemical formula: $C_{17}H_{19}ClN_2S \cdot HCl$
Pharmacologic/therapeutic categroy: Anti-emetic, antipsychotic
Reference: USP 23, page 354
Structural formula:



16. RECORDS AND REPORTS
None

17. COMMENTS

This application is approvable.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: Liang-Lii Huang, Ph.D. DATE COMPLETED: December 22, 1998

Endorsed by Paul Schwartz, Ph.D./ January 15, 1999

cc:

ANDA 40-224
ANDA DUP 40-224
DIV FILE
Field Copy
HFD-600 /Reading File

Endorsements:

HFD-627 / Liang-Lii Huang, Ph.D./ 12/23/98; 1/14/99
HFD-627 /Paul Schwartz, Ph.D./ 1/15/99 PS 1/14/99

1/14/99

C:\WPFILES\40224N01.RV3

F/T by: bc/1-5-99

CHEMISTRY REVIEW - APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40224

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #40-224
SPONSOR: Pharmaceutical Associates, Inc.
DRUG: Chlorpromazine HCl
DOSAGE FORM: Oral Concentrate
STRENGTH: 100 mg/mL
REFERENCE PRODUCT: SmithKline Beecham's Thorazine® Oral Concentrate 100 mg/mL.
SUBMISSION TYPE: Waiver

STUDY SUMMARY: Not Applicable

DISSOLUTION: Not Applicable

WAIVER SUMMARY: The waiver of the *in vivo* bioequivalence study for the test product, Chlorpromazine HCl Oral Concentrate, 100 mg/mL is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product formulation to be bioequivalent to the reference drug SmithKline Beecham's Thorazine® Oral Concentrate 100 mg/mL.

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III

INITIAL: /S/ DATE: 4/10/97

ROUP LEADER: Ramakant Mhatre, Ph.D. BRANCH: III

INITIAL: /S/ DATE: 4/17/97

---

for DIRECTOR: Nicholas Fleischer, Ph.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 5/19/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: _____ DATE: _____

MAY 13 1997

Chlorpromazine HCl
Oral Concentrate, 100 mg/mL
ANDA #**40-224**
Reviewer: Z.Z. Wahba
File# 40224w.n96

Pharmaceutical Associates, Inc.
Greenville, SC
Submission Date:
November 25, 1996

REVIEW OF A WAIVER REQUEST

I. BACKGROUND

The firm has requested a waiver of in vivo bioavailability study requirements for its drug product, Chlorpromazine Hydrochloride Oral Concentrate, 100 mg/mL. The reference drug product is SmithKline Beecham's Thorazine® Oral Concentrate 100 mg/mL.

II. FORMULATION COMPOSITION (should not be released under FOI)

Ingredient	mg/mL
Chlorpromazine HCl, USP	100 mg
Saccharin Sodium, USP	mg
Sodium Benzoate, NF	mg
Edetate Calcium Disodium	mg
Citric Acid, USP	mg
Ascorbic Acid, USP	mg
Sodium Bisulfite,	mg
Glycerin, USP	mL
Propylene Glycol, USP	mL
Vanilla	mL
Sodium Hydroxide, NF	to adjust pH
Purified Water, USP q.s. to	mL

Note: the reference product contains the following inactive ingredients: calcium disodium edetate, citric acid, flavors, hydroxypropyl methylcellulose, propylene glycol, saccharin sodium, sodium benzoate, water and trace amounts of other inactive ingredients.

III. COMMENTS

1. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".

2. The test drug product does not contain any inactive ingredient(s) that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

3. The concentrations that are provided in the statement of chemical composition for all the inactive ingredients except edetate calcium disodium and citric acid fall in the acceptable range of the Agency's Inactive Ingredient Guide. For edetate calcium disodium concentration, once it is diluted as specified in the drug labeling (each dose to be diluted in 60 mL water or fruit juice) the percentage of the concentration falls in the acceptable range of edetate calcium disodium oral solution that is reported in the Agency's Inactive Ingredient Guide. Citric acid is a natural product and present in a lot of food produces and products. Vanilla is used as a flavoring ingredient. Concentrations of citric acid and vanilla that are provided in statement of chemical composition should not cause any safety problems.

4. The waiver of in vivo bioequivalence study requirements should be granted based on 21 CFR section 320.22(b)(3) of the Bioavailability/Bioequivalence Regulations.

IV. RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Pharmaceutical Associates, Inc. for its drug product, chlorpromazine Hydrochloride Oral Concentrate, 100 mg/mL, falls under 21 CFR section 320.22(b)(3) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the drug is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems chlorpromazine Hydrochloride Oral Concentrate, 100 mg/mL, manufactured by Pharmaceutical Associates, Inc. to be bioequivalent to the reference product, SmithKline Beecham's Thorazine® Oral Concentrate 100 mg/mL.

The firm should be informed of the recommendation.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ 5/13/97

Concur: /S/ Date: 5/13/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA# 40-224, original, HFD-630 (OGD), HFD-604, HFD-658 (Mhatre, Wahba), Drug File
ZZWahba/040497/041097/050797/file #40224w.n96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40224

CORRESPONDENCE

ANDA 40-224

MAY 20 1997

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
P.O. Box 128
Conestee, SC 29636

Dear Madam:

Reference is made to your abbreviated new drug application submitted November 25, 1996, pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Chlorpromazine HCl Oral Concentrate, 100 mg/mL.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

pai Pharmaceutical Associates, Inc.

12-31-96

1/13/97

November 25, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA Chlorpromazine Hydrochloride Concentrate 100mg/mL

Dear Sir:

Enclosed is the abbreviated new drug application for the drug product Chlorpromazine Hydrochloride Concentrate 100 mg/mL in 16 oz and 8 oz containers and a 16 oz glass container.

We have answered comprehensively, responsibly, and to the best of our ability all required items on Form FDA 356h and have to the best of our knowledge replied to the requirements of 21 CFR Section 314.50 and 314.94 where applicable.

The Table of Contents explains the organization of the application which consists of two volumes. Volume 1 consists of Sections I-XIV and Volume 2 consists of Sections XV-XXI. Each separate section of the ANDA is split off by labeled dividers that contain both the section number of that section and brief description of the section's subject matter (e.g., I. Basis). These dividers correspond to the sections listed in the Table of Contents.

Pharmaceutical Associates, Inc. is filing an archival copy (in blue folder) that contains all the information required in the ANDA and a technical review copy (in red folder) which contains all the information in the archival copy. In addition, we are also providing, in yellow folders, three additional copies of the methods validation portion of the ANDA.

I certify that a true copy of this application has been provided to the Atlanta District Office.

Thank you for your consideration in this matter.

Sincerely yours,

PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Scientific Affairs Manager

pai Pharmaceutical Associates, Inc.

April 14,1998

RECEIVED

APR 20 1998

GENERIC DRUGS

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: 40-224 Chlorpromazine Hydrochloride Oral Concentrate USP, 100 mg/mL.

The following is in answer to the major deficiency amendment of June 24, 1997.

A. Deficiencies:

1. DMF was found to be inadequate. The DMF holder has been notified.

   Response: the holder of DMF has assured us that the deficiencies have been addressed.

2. The expression in percentage for the formula composition of the Chlorpromazine Hydrochloride Oral Concentrate USP, glycerin USP is expressed in %v/v and saccharin sodium, sodium benzoate, edeteate calcium disodium, citric acid, ascorbic acid and sodium bisulfate are expressed in %w/v in the same formula. Please provide the consistent percent expressions for the formula of the subject product.

   Response: The formula composition statements have been revised to include % v/v for all liquids and % w/v for all solids. We measure liquids such as glycerin and propylene glycol by volume and weigh all solids. Revised composition statements are included on pages 1-7 of this amendment.

3. In the manufacturer's certificate of analysis for chlorpromazine hydrochloride drug substance, two numbers are given % and %, under the item color. Please explain.

Response: The manufacturer has informed us that the two numbers under item color are information that is requested by another customer and is of no significance to us. The numbers do represent transmittance at two different wavelengths.

4. Your stated fill volumes at LCL, target and UCL are consistently above the calculated results using the density of the chlorpromazine HCl oral concentrate g/mL) provided in the application. Please see the calculation given below using the LCL data as an example on page 267.

(Gross wt) – (container wt) = Net wt
g (LCL) – g = g

(Net wt) divided by (density) = calculated fill volume
g/ g/mL = mL

Your stated fill volume is mL, not mL. Please clarify this discrepancy and others identified by using target and UCL data.

Response: For a trade package the label claim is used as our lower control limit. The target and upper control limit are established at levels to ensure that the bottle held at least the labeled amount. In your example you are using g as the container weight while it should be g:
LCL mL

(Gross wt.) – (container wt) = Net wt
g (LCL) – g = g

(Net wt) divided by density = calculated fill vol
g/ g/mL = mL

Target mL
g – g = g

g/ g/mL = mL

UCL mL
g – g = g

g/ g/mL mL

5. On page 560, under the system suitability test, resolution is not less than 1.2 between the sodium benzoate peak and the previous peak. It is not clear which one is the previous peak. Please specify the retention time to identify the peak to be used for calculating the resolution factor.

   Response: The method has been revised to clarify the peak to be used to calculate the resolution factor. The revised method is included on pages 8 - 16 of this amendment.

6. In addition to the RSD and peak tailing factor, three parameters, i.e., capacity factor, number of theoretical plates (column efficiency), and resolution factor should also be calculated and reported in the system suitability tests.

   Response: Capacity factors, number of theoretical plates and resolution factor have been added to the system suitability tests. The revised method is included on pages 8 - 16 of this amendment.

7. Please provide available room temperature (25° - 30°C) stability data for the Chlorpromazine HCl Oral Concentrate USP, 100mg/mL (lot #13818) stored in the glass containers.

   Response: All available room temperature stability data for the 8 oz. is included on page 17 of this amendment. Due to marketing considerations, we wish to withdraw the 16oz container at this time. The following pages for the 16oz. size can be disregarded.

   Pages 48-56
   310-380
   636-639

8. Please explain the reason why sodium benzoate should go to % for the stability samples.

   Response: Sodium Benzoate is not expected to go to % for stability. The limits have been revised with the revised stability specifications included on pages 18 - 19 of this amendment.

9. Please provide the limits for other individual and total impurities of the finished product at the time of product release and for stability.

   Response: The limits for other and total impurities are provided in the release and stability specifications on pages 20 - 21 of this amendment.

10. Please provide a quantitative color specification for the finished product and stability samples.

Response: A quantitative color specification has been developed and is included as part of the method on pages 8 - 16. The shelf stability samples were tested at 18 months. The results are on page 22.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your ANDA application relative to the drug substance and drug product manufactures, packaging and stability testing must be in compliance with cGMP's at the time of approval.

Response: We acknowledge that the firms referenced in the ANDA application relative to the drug substances and drug product manufacture packaging and stability testing must be in compliance with CGMP; s at the time of approval.

2. Your analytical methodology is not identical to the US Pharmaceutical methods for the final drug product. Please be advised that the USP methods are the regulatory methods and will prevail in the event of any dispute.

Response: We acknowledge that our analytical methodology is not identical to the US Pharmacopial methods for the final drug product and that the USP methods for the final drug product. Please be advised that the USP methods are the regulatory methods and will prevail in the event of any dispute.

LABELING DEFICIENCIES

1. **Container:** We wish to withdraw the 16-oz. container at this time due to marketing considerations. The following pages for the 16oz. size can be disregarded.

Pages 48-56
310 – 380
636 – 639

Our 30mg/mL will use green for labeling and carton, and the 100 mg/mL will be red.

pai Pharmaceutical Associates, Inc.

On pages 49 - 52 are 2x12 copies of final print for our container labels incorporating all of your comments.

2. **Carton:** On pages 59 - 70 are 2x12 copies of final print for our cartons incorporating all of your comments.

3. **Inserts:** On page 53 - 58 are 2 x 12 copies of final print for our insert.

A side by side comparison of our proposed labeling and our last submission is included on pages 23 - 48.

We have answered all of your questions to the best of our knowledge. If you have further questions, please let us know.

Sincerely Yours,
PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs

pai Pharmaceutical Associates, Inc.

MINOR AMENDMENT

N/AM

November 30,1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: 40-224 Chlorpromazine Hydrochloride Oral Concentrate USP, 100 mg/mL.

The following is in answer to the minor deficiency amendment of September 22, 1998.

A. Deficiencies:

1. DMF remains inadequate. The DMF holder has been notified. Please do not respond until the DMF holder has notified you that they have answered to their deficiencies.

   Response: We have been notified by the DMF holder that the deficiencies have been addressed. A copy of their letter is included on page 1.

2. Please provide the analytical methods to be used for examing the individual impurities and total impurities, for example, method, conditions and its entire procedure including relevant calculation and chromatograms. Please also provide the certificate of analysis to support the proposed specifications for the impurities, i.e., COA of the drug substance from the drug manufacturer and Pharmaceutical Associates, Inc., and COA of the drug product and stability data.

   Response: The analytical method for examing the individual and total impurities is included in our test method Section III pages 2-4. A copy is included on pages 2-10. Representative chromatograms are on pages 11-12. The COA for the drug substance from the drug manufacturer is included on page 14. They have a limit for a single impurity of NMT %. USP has a limit of NMT % for other alkylated phenothiazines in the drug substance. Our proposed limits for the drug product for Chlorpromazine Sulfoxide are not more than % initially and not more than % for stability. These are based on the USP limit for the sulfoxide of NMT %. Our limit for other individual impurities for release of NMT % and total of % are based on the raw material limit of % for individual impurities.

A COA for the drug product is included on page 16. The USP method for sulfoxide was run at that time. When the alternate method was developed, the 16 oz. glass bottle P-361 was tested. The sulfoxide was at 0,4 and for other impurities there were none detected. Stability data showing impurities is included on pages 17-18.

3. On page 127 of the original application, under heavy metals and chromatographic purity, the results reported as "conform" are not acceptable. The quantitative test data should be given in the certificate of analysis. The analytical method, for example, or USP 23, should be provided for each test in the report form.

Response: The certificate of analysis for the drug substance has been revised and appears on pages 19-20.

B. Labeling Deficiencies

1. **Container:** Revised container labeling (2x12 copies) incorporating all of your comments is in pages 29 – 32.

2. **Carton:** Revised carton labeling (2x12 copies) incorporating all of your comments is in pages 39 – 50.

3. **Insert:** Revised insert (2x12 copies) incorporating all of your comments is in pages 33 – 38.

We have answered all of your questions to the best of our knowledge. If you have further questions, please let us know.

Sincerely Yours,
PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs

pai Pharmaceutical Associates, Inc.

FACSIMILE AMENDMENT

December 22, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/An 1

RE: ANDA 40-224 Chlorpromazine HCl Oral Concentrate USP 100 mg/mL

Attn: Dr. Paul Schwartz

In response to our telephone conversation of yesterday afternoon, I have enclosed copies of our revised testing specifications for Raw Material, Bulk Product, Packaged Product, and Stability.

We will follow with hard copies of all pages enclosed.

If you have any further questions, please do not hesitate to call.

Sincerely,
PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs

1998

Beach Products, Inc. Contract Sales
5220 South Manhattan Avenue
Tampa, FL 33611
Phone: (813) 839-6565
Fax: (813) 837-2511

Leadership and Integrity
Since 1958

Pharmaceutical Associates Subsidiary
201 Delaware Street
Greenville, SC 29605
Phone: (864) 277-7282
Fax: (864) 277-8045

pai Pharmaceutical Associates, Inc.

FACSIMILE AMENDMENT

January 13, 1999

NDA [illegible] AMENDMENT

AM

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 40-224 Chlorpromazine HCl Oral Concentrate USP 100 mg/mL

Attn: Dr. Joseph Buccine

In response to our telephone conversation of yesterday afternoon, I have enclosed a copy of our revised testing specifications for the Raw Material.

We will follow with hard copies of all pages enclosed.

If you have any further questions, please do not hesitate to call.

Sincerely,
PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs

RECEIVED
JAN 21 1999
[illegible]

Beach Products, Inc.-Contract Sales
5220 South Manhattan Avenue
Tampa, FL 33611
Phone: (813) 839-6565
Fax: (813) 837-2511

Leadership and Integrity
Since 1958

Pharmaceutical Associates Subsidiary
201 Delaware Street
Greenville, SC 29605
Phone: (864) 277-7282
Fax: (864) 277-8045

pai Pharmaceutical Associates, Inc.

FACSIMILE AMENDMENT

January 11, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 40-224 Chlorpromazine HCl Oral Concentrate USP 100 mg/mL

Attn: Dr. Paul Schwartz

In response to our telephone conversation of this afternoon, I have enclosed revised copies of our revised testing specifications for Raw Material, Bulk Product, Packaged Product, and Stability.

We will follow with hard copies of all pages enclosed.

If you have any further questions, please do not hesitate to call.

Sincerely,
PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40224

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

Reference is made to the fax amendment dated December 16, 1998.

Dr. Schwartz and Dr. Huang called the sponsor requesting the following information:

The impuritiy specifications should be provided in a table format for the drug substance, drug product release and stability.

Your complete response should be submitted as a fax amendment.

Ms. McDonald called agreed.

cc:
ANDA
Division File
T-con Binder

X:\NEW\FIRMSNZ\PHARMACE\TELECONS\40224CON.001

DATE
December 21, 1998

ANDA NUMBER
40-224

IND NUMBER

TELECON

INITIATED BY FDA

PRODUCT NAME
Chlorpromazine hydrochloride Oral concentrate, 100 mg/mL

FIRM NAME
Pharm Associates

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Kaye McDonald

TELEPHONE NUMBER
864 277 7282

SIGNATURE
Liang-Lii Huang
/S/

RECORD OF TELEPHONE CONVERSATION

Reference is made to the fax amendment dated December 22, 1998.

Dr. Schwartz and Dr. Huang called the sponsor requesting the following information:

1. Microbial limits test was not included in the product release and stability on Pages 3, 4, and 5.

2. This is a USP product. The USP ID tests should be followed. Please provide USP ID tests in the bulk product and packaged product release.

3. The references should be provided for analytical methods.

4. The assay value for the chlorpromazine hydrochloride should be reported as % . (missing one decimal point)

Your complete response should be submitted as a fax amendment.

Ms. McDonald called back and agreed.

cc:
ANDA
Division File
T-con Binder

X:\NEW\FIRMSNZ\PHARMACE\TELECONS\40224.001

DATE
January 11, 1999

ANDA NUMBER
40-224

IND NUMBER

TELECON

INITIATED BY FDA

PRODUCT NAME
Chlorpromazine hydrochloride Oral concentrate, 100 mg/mL

FIRM NAME
Pharm Associates

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Kaye McDonald

TELEPHONE NUMBER
864 277 7282

SIGNATURE
Liang-Lii Huang
/S/